Iotasul, A Water-soluble (Non-oily) Contrast medium for Direct and Indirect Lymphography

Radiological and morphological investigations in dogs

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Summary

Radiological, light microscopic and electron microscopic findings after direct and indirect lymphography with Iotasul, a new non-ionic water-soluble (not oily) contrast medium, are reported. The results of the studies in 18 dogs clearly show that the roentgenological demonstration of the lymph system following intralymphatic administration of Iotasul in the dog is not inferior to that following the use of conventional oily con contrast medium passes quickly to the lymphatic system and the lymph nodes and is eliminated within 24 hours. The complications and tissue reactions known from oily contrast media are not observed following use of the new water-soluble contrast medium. Furthermore, studies of the fine structures show unequivocally that no morphologically detectable changes attributable to the contrast medium occur either in the region of the injection or in the lymph vessels, lymph nodes and organs such as kidney, liver, lung, spleen and myocardium. Preliminary studies indicate that the new contrast medium offers the possibility of indirect demonstration of lymph vessel regions and groups of lymph nodes (indirect lymphography) which have largely escaped detection by the previous routine lymphographic examination.

Introduction

The possibilities and limitations of direct lymphography with oily contrast media, which was introduced to clinical use by *Kinmonth* in 1952, have been described in detail over the last 3 decades (*Kaindl* et al. 1960; *Fuchs* 1965; *Rüttimann and Wirth* 1968; *Gerteis* 1972; *Gregl* 1975; *Müller* 1979). The limitations of the method are set by the nature of the contrast medium, which can elicit pronounced foreign body reactions and also lead to allergic reactions and embolic complications. Diagnosis of the lymphatic system is further limited by the necessity to administer the contrast material via the lymph vessels, which means that individual lymph node groups and lymphatic systems are not routinely accessible and, hence, cannot be demonstrated radiologically.

This situation can be remedied by the use of indirect lymphography, in which opaque substances are introduced into the interstice of the skin, subcutis, muscles, parenchymatous organs or in serous cavities without surgical intervention. Indirect lymphography with iodinated oils or iodized oil emulsions has been the subject of numerous animal-experimental studies. Although, with some routes of administration, emulsions proved to be superior to iodinated oils as regards the quality of the contrast, the local and general tolerance was considerably poorer.

Attempts at indirect lymphography with iodinated oils in man bore no clinical fruit (*Renziehausen and Schmeissser* 1968; *Comino* et al. 1969; *Kett* et al. 1970; *Schacht* et al. 1974; *Smyrnis* et al. 1975; *Wesirow and Lüning* 1976; *Schacht* et al. 1976; *Gandhi and Shanker* 1976; *Gandhi* 1977; *Wesirow* et ·

Sanatger 1978; *Böcker and Huth* 1978; *Raghavaiah and Jordan* 1979).

Apart from oily contrast media, crystal suspensions of difficult-to-dissolve contrast media for indirect lymphography have also been studied in animals (*Felder* et al. 1977; *Kaude* et al. 1978). Although the results obtained with some of these compounds were very good as regards picture quality, the local tolerance again proved to be the limiting factor for studies in man.

Iotasul, a water-soluble contrast medium for direct and indirect lymphography, was first described by *Siefert* et al. (1980). In animals, the substance is marked by rapid renal excretion, good systemic tolerance and excellent suitability for roentgenology.

The object of the present studies is to demonstrate the systemic tolerance of this new contrast medium by morphological findings made with the light and electron microscope after direct and indirect lymphography, and to describe the radiological results.

Material and Methods

The contrast medium used — the non-ionic dimerous hexaiodinated contrast medium Iotasul* — was available as an aqueous formulation with an iodine content of 275 mg/ml.

The studies were conducted in 18 male and female beagle dogs with a body weight of 9—25 kg. In a first series of 8 dogs, between 5 and 15 ml of the contrast material were administered over a period of 20—60 min. with the aid of an infusion pump into a superficial lymph vessel of the pelvic extremity following demonstration by patent blue injection and exposure caudal of the knee joint. The infusion was given on an X-ray table to permit continuous supervision of the contrast medium accumulation. Films were made in the period 5—120 min. after the start of infusion and 24 hours, 3 and 8 days after the infusion. Preparation of the lymph vessels and infusion of the contrast material were performed under general anaesthesia with chloralose, Nembutal® and Valium® or with Rompun and Ketanest.

2 Dogs of this series were anaesthetized at each of the times 1 hour, 24 hours, 3 and 8 days after administration and the following tissues and organs removed for light and electron microscopic examinations: injection region, popliteal lymph nodes, pelvic lymph nodes, thoracic duct, mediastinal lymph nodes, kidneys, liver, spleen, right and left heart and lungs

In a second series of 5 dogs, 1—2 ml of contrast medium were administered intracutaneously over a period of 5—30 min. with the aid of an infusion pump at 2—5 different sites of the paw of the pelvic extremity. 1 dog was anaesthetized at each of the times 1 hour, 24 hours, 3 and 8 days after application and the above-mentioned tissues and organs removed; in 1 dog, the organ and tissue specimens were not removed until after 6 months.

In a third series of 3 dogs, the contrast medium was administered at an amount between 3 and 10 ml once unilaterally and submucosally into a lip, once bilaterally and submucosally into the lips and, finally, sublingually and submucosally by infusion. In these dogs, the injection regions, the other tissues and the above-mentioned organs were removed under narcosis 24 hours, 3 and 8 days after administration.

One control animal received an infusion of 5 ml Lipiodol® Ultra Fluid* into a superficial lymph vessel of each of the two pelvic extremities — as described above — over a period of 30 min. The organ and tissue specimens were removed from this animal 8 days after administration. A second control dog received 10 ml/Ringer's lactate solution intralymphatically over a period of 25 min. in the manner described. The organ and tissue specimens were likewise removed 8 days after administration.

The tissues and organs were fixed in 4 % formalin and embedded in paraffin for the light-microscopic studies; the paraffin sections were stained as follows:
Haematoxylin-eosin; iron haematoxylin-picrofuchsin after *van Gieson* combined with resorcin; PAS reaction and the Berlin blue reaction. In addition, frozen sections of some organs were treated with Sudan red.

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*Byk Gulden, Konstanz a.B.

For the electronmicroscopic studies, the kidneys were fixed with perfusion by glutaraldehyde following brief rinsing with isotonic saline solution. The other organs were fixed following immersion in 2% buffered glutaraldehyde. Subsequent fixing with buffered osmium tetroxyde was performed for the transmission electron microscopic studies. Semi-thin sections of tissue pieces embedded in araldide were stained with methylene blue. The ultra-thin sections were subsequently enhanced with uranyl acetate and lead citrate. Following perfusion fixation and subsequent immersion fixing, the thoracic ducts were checked under an electron scan microscope.

Clinical observations

Neither during infusion of the contrast medium nor during the subsequent observation periods were any disturbances of the cardiovascular system or signs of an embolic process observed. There were neither wound infections following preparation of the lymph vessels in the first group of animals nor macroscopically perceptible changes in the cutaneous or intramucous injection region in the other two groups. Similarly, there were no signs of pneumonic complications or other general infections. None of the animals refused food or displayed excretory disorders following infusion of the contrast medium.

Radiological findings

Rapid opacification of the lymph vessels of the lower leg were observed under fluoroscopic control during the intralymphatic infusion of the contrast material. The popliteal lymph nodes began to opacify after 10–15 min. and popliteal and femoral lymphatic vessels including their delicate valvular constrictions became visible at the same time (Fig. 1b). The pelvic lymphatic vessels and first pelvic lymph nodes (external iliac lymph nodes) were demonstrated after 20–30 min. (Fig. 1a). The chylocyst (Fig. 1e) above the lumbar lymphatic trunks and in mostly places, the thoracic duct as well (Fig. 1c) were visible at the latest after 45 min. In some dogs, the segmental narrowing of the thoracic duct caused by its valves was demonstrable as far as the venous angle (Fig. 1f).

Because of the rapid renal elimination of the contrast material, the pelvicalyceal system and the point of transition of the renal pelvis to the ureter were occasionally faintly recognizable in the X-ray film within the first 30–60 min.

After some practice, it became clear that as little as 5 ml of the contrast medium were frequently sufficient to demonstrate the lymphatic system of the dogs from the pedal lymphatic vessels through the popliteal lymph nodes, the pelvic lymph nodes, the lumbar trunks, the chylocyst and the thoracic duct to the venous angle.

Similarly, it was found after some practice that the above-mentioned lymphatic vessels and lymph nodes could also be demonstrated following intracutaneous infusion of the contrast medium into the paw of the pelvic extremity. For example, the popliteal lymph nodes were demonstrated within only 5 min. of the start of infusion in two animals (Fig. 1d). The first pelvic lymphatic vessels and pelvic lymph nodes up to the lumbar lymphatic trunks were usually recognizable after more than 20 min. Opacification of the thoracic duct up to its emergence through the diaphragm occurred under this form of application about 30 min. after the start of the infusion.

Submandibular and cervical lymphatic vessels leading to a weakly enhanced cervical lymph node were opacified only 30 min. after a slow infusion of 3 ml Iotasul under the epithelium of a lip (Fig. 2a). Corresponding opacification of other lymphatic vessels or lymph nodes of the neck failed to take place in this dog. The submandibular lymphatic vessels began to fill only 10 min. after infusion of 2 ml Iotasul into each lip. Bilateral lymphatic reticular and supralaryngeal lymph nodes including an efferent lymphatic vessel were visualized after 20 min. (Fig. 2b). Comparable radiological findings were obtained following a slow sublingual infusion into the mucosa of 3.5 ml at each of three sites.

Comparison of the lymphograms both after intralymphatic and after intracutaneous infusion shows clearly that no particular roentgenological differences exist between the findings
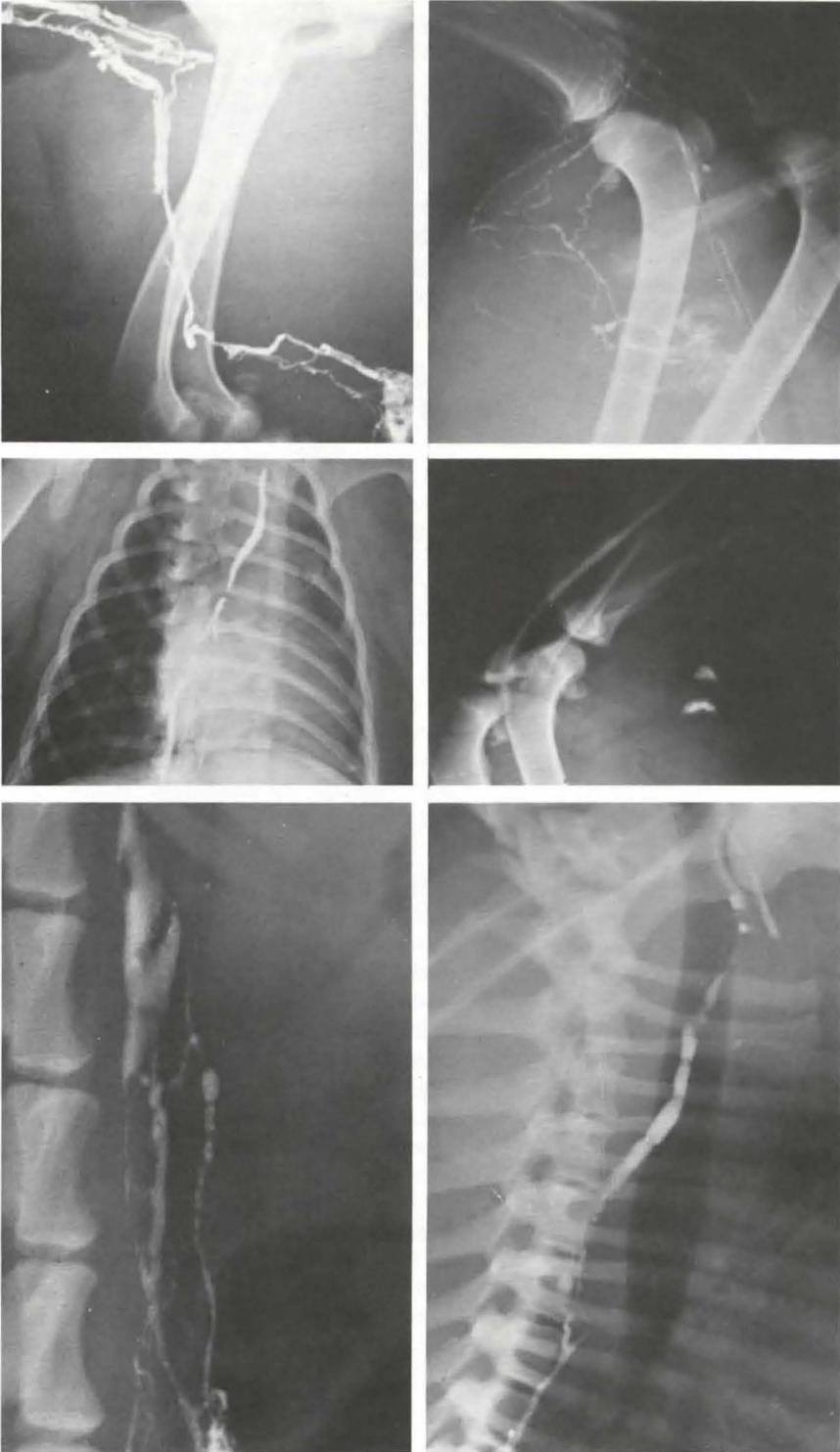
Fig. 1a—f
(Description
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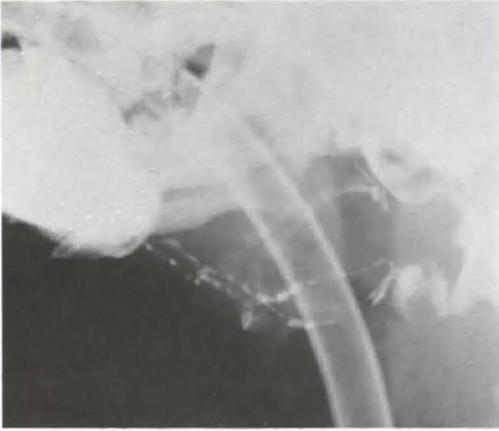
Fig. 2a Submandibular and cervical lymphatic vessels with beginning demonstration of a cervical lymph node 30 minutes after submucous infusion of Iotasul into the left lip

Fig. 2b Submandibular lymphatic vessels and demonstration of cervical lymph nodes 22 minutes after submucous infusion of Iotasul into both lips

from the two methods of administration. Moreover, there are also no differences in the quality of the roentgenological demonstration between these and lymphograms made after administration of a conventional oily contrast medium.

As was to be expected, no radiologically detectable findings were made following infusion of Ringer's lactate solution.

Distinct differences do, however, exist between Iotasul and the oily contrast medium as regards the rate of excretion: while it has long been known that the oily contrast medium is stored persistently in the lymph nodes over a long period of time, Iotasul could not be demonstrated radiologically in any of the 16 dogs 24 hours after administration of the contrast medium.

Findings from the lightmicroscopic studies

For better comparison, the findings from the control animals are described first: no pathological changes can be detected by light microscopy following intralymphatic infusion of Ringer's lactate solution (this animal was not studied by electronmicroscopy).

Histological controls 8 days after intralymphatic infusion of a conventional oily contrast medium reveal the typical storage reactions at the lymphatic vessels and the storing popliteal, pelvic and paraaortic lymph nodes; they consist in the lymph vessels of xanthoma-cell conversion of individual endothelial cells with the formation of individual foreign body giant cells in the endothelium and of a pronounced histiocytic and giant-cell foreign body reaction

Fig. 1a—f:

1a) Popliteal lymph nodes and femoral and pelvic lymphatic vessels 30 minutes after intralymphatic infusion of Iotasul

1b) Dense network of popliteal lymphatic vessels 15 minutes after intralymphatic infusion of Iotasul

1c) Demonstration of the thoracic duct 45 minutes after intralymphatic infusion of Iotasul

1d) Demonstration of dual popliteal lymph nodes 5 minutes after intracutaneous infusion of Iotasul

1e) Demonstration of the lumbar lymphatic trunks and the chylocyst 45 minutes after intralymphatic infusion of Iotasul

1f) Demonstration of the thoracic duct and its valvular structures up to the venous angle 45 minutes after intralymphatic infusion of Iotasul
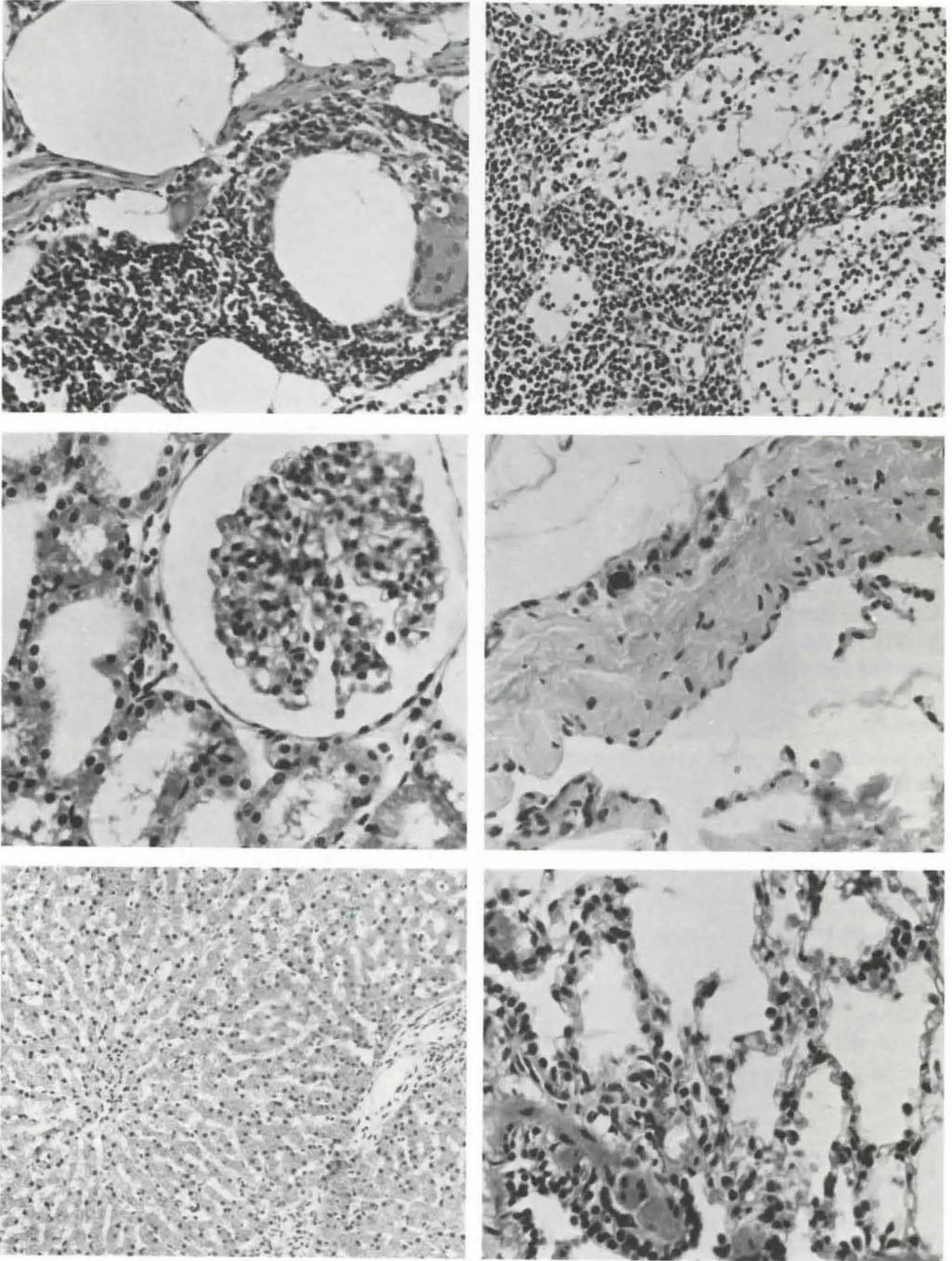
Fig. 3a–f

3a) Section of a pelvic lymph node with coarse vacuolar loosening of the lymphatic tissue and giant-cell for-
    eign body reaction 8 days after intralymphatic pedal infusion of an oily contrast medium. HE, 100 x
3b) Section of a popliteal lymph node with wide sinus but without any particular pathological changes 24
    hours after intracutaneous pedal infusion of Iotasul. HE, 100 x
(Continuation next page)

around the primarily oilfilled pseudocysts within the storing lymph nodes (Fig. 3a). No contrast medium embolisms or their sequelae were observed in any of the tissues or organs examined following administration of the oily contrast medium. No electron microscopic studies of the storage phenomena following use of the oily contrast medium were performed because of the adequate documentation in the literature.

No morphologically detectable differences in the individual tissues and organs studied exist within the three study groups following intralymphatic, intracutaneous and intramucosal administration of Iotasul. Consequently, the following histological description applies to all three groups. A bland inflammatory reaction with sparse granulocytic, lymphocytic and macrophagocytic cells is occasionally observed in the region of the infusion following preparation of a pedal lymphatic vessel; it is only slight after 3 days and has disappeared after 8 days. Comparable bland inflammatory infiltrations which likewise regress within the first 8 days are also observed following intracutaneous and intramucosal infusion of the contrast medium.

No lymphangitic changes are demonstrable either immediately above the infusion region or at the other ascending lymphcollecting vessels of the lymphatic trunks. In none of the groups studied are there any signs of alteration of endothelial cells or valves in the sense of storage phenomena (Fig. 3d). Like the cervical lymph nodes, both the popliteal and the pelvic lymph nodes sometimes display relatively wide sinuses following contrast medium infusion (Fig. 3b). However, similarly wide sinuses are also demonstrable in the control animal following infusion of Ringer's lactate — and also within mediastinal lymph nodes, for which no contrast medium passage can be assumed. No lymphadenitic infiltrates, swelling of marginal cells of the sinuses or storage phenomena are demonstrable in any of the lymph nodes studied following administration of Iotasul. Similarly, there are no light microscopic indications of an immunological reaction within the lymphatic tissue. The contrast medium cannot be detected morphologically either within the lymphatic vessels or in the lymph nodes. The same is true for the other organs.

The excretory organ kidney displays no changes detectable by light-microscopy in any of the observation phases of the study. In particular, there are no changes of the loop apparatus of the glomeruli including the glomerular tegumentary epithelium or of the epithelium of the main body (Fig. 3c). The deeper sections of the nephron, the renal interstice and the renal blood vessels also display no pathological changes detectable by light-microscopy.

The liver preparations examined likewise display no changes of the hepatocellular liver parenchyma or of the biliary tract. No storage reactions are demonstrable in the marginal cells of the sinuses, and there are likewise no inflammatory changes of the hepatic septa. No toxic reactions such as liver cell necroses, fatty degeneration or cholestatic phenomena are demonstrable, either (Fig. 3e).

The representative sections from various pulmonary lobes display normal ventilation and a delicate structure of the alveolar septa in all phases of the study. Like the larger pulmonary vessels, the alveolar capillaries are free from embolic obstruction. There are no inflammatory reactions either in the interstitial connective tissue or in the parietal structures of the intersected bronchi (Fig. 3f).

Continuated legend Fig. 3a–f:

3c) Normal adrenocortical tissue with delicate glomerular and tubular structures 24 hours after intralymphatic infusion of Iotasul. HE, 150 x.

3d) Parietal section of a thoracic duct with normal parietal structures, flat endothelium and delicate valvular section 24 hours after intralymphatic infusion of Iotasul. HE, 250 x

3e) Normal hepatic lobe and section of a portal septum without pathological finding. 24 hours after intralymphatic infusion of Iotasul. HE, 100 x

3f) Inconspicuous structures of the alveolar wall above the section of a bronchiolus of the lung 24 hours after intralymphatic infusion of Iotasul. HE, 250 x

Fig. 4a Electron scan microscopic picture of delicate collapsed valvular offshoots and an intact endothelium of the thoracic duct 3 days after intralymphatic pedal infusion of Iotasul; 450 x

Fig. 4b Transelectron microscopic section of a renal glomerulus with intact loop structures 24 hours after intralymphatic pedal infusion of Iotasul; 5,500 x

The splenic preparations examined display the hyperaemic red pulp characteristic for dogs. In none of the dogs are the follicles enlarged. Neither storage phenomena nor inflammatory reactions are demonstrable within the red pulp.

No changes are recognizable in the heart sections; both the endothelia of the coronary vessels and the endocardium are flat in all cases and devoid of storage reactions and inflammatory infiltrates.

Findings from the electron microscopic studies

There are likewise no differences in the electron scan and transmission microscopic findings between the three groups with Iotasul, so the findings can again be dealt with together.

As regards the lymphatic vessels, the electron microscopic studies were concentrated mainly on the endothelium. In none of the study groups are storage phenomena demonstrable either in the endothelial cells of the peripheral lymphatic vessels or in those of the trunks (Figs. 4a and 5a); there are likewise no changes of the valvular structures within the efferent lymphatic system up to the thoracic duct (Fig. 5a). No lysosomal particles or vesicular structures of the
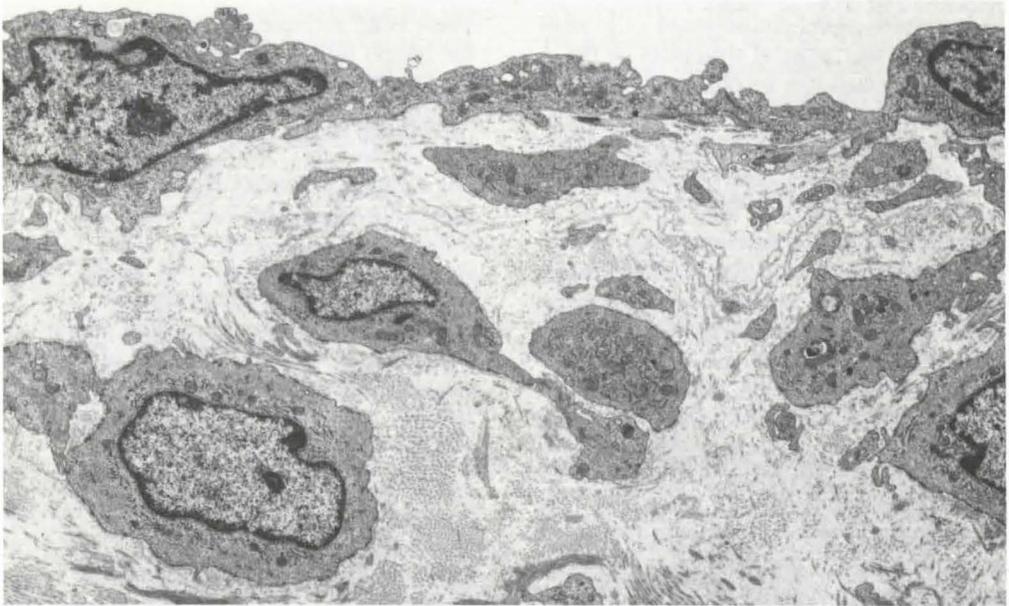
5a)
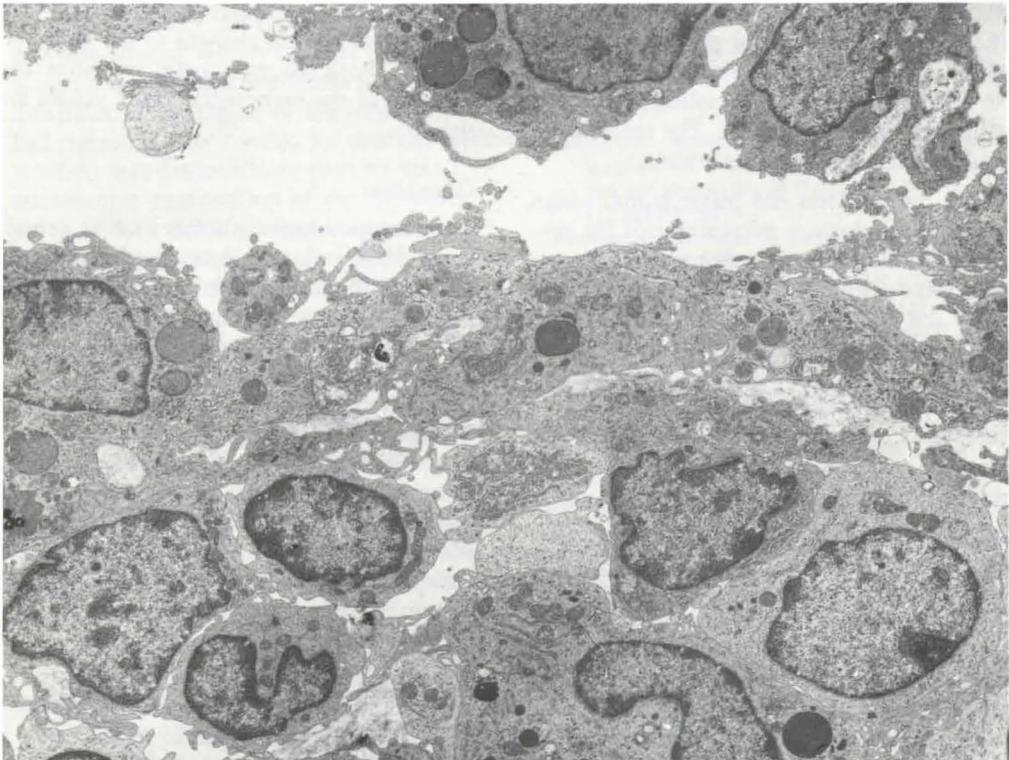
5b)

Fig. 5a Transelectron microscopic picture of the wall of a lymph-collecting vessel with intact endothelium and loose parietal structures 3 days after intralymphatic pedal infusion of Iatosul, lymph-collecting vessel from the injection region; 6000 x
Fig. 5b Transelectron microscopic picture of a popliteal lymph node sinus without pathological finding 24 hours after pedal intracutaneous infusion of Iotasul; 4500 x

the lymphatic vessel endothelium or loosening of the other parietal structures of the lymphatic vessels can be observed (Fig. 5a). Similarly, there are no signs of inflammatory or immunological reactions within the wall of the lymphatic vessels which could be ascribed to contact with the contrast material.

The structures of the capillary walls within the renal glomerulae display a delicate endothelium, even basal membranes, delicate, foot-shaped processes of the tegumentary epithelium and an inconspicuous mesangium (Fig. 4b). The ciliated border of the main bodies is intact, and the elongated mitochondria display uniform crista and membrane structures. The lysosomes of the epithelium of the main bodies are neither increased nor enlarged. There are no storage vacuoles or enlarged cytosegresomes. The rest of the epithelium of the nephrons does not differ from that of the control animal.

There is no widening of the renal interstitium, which is free from inflammatory cell infiltrates. No xanthomatous transformation of the interstitial cells can be observed. The renal vessels display delicate parietal structures.

Within the popliteal and pelvic lymph nodes, transmission electron microscopy of the representative sections reveals normal composition both within the follicular structures and under the cells within the sinuses. The marginal cells of the sinuses have not undergone any alteration (Fig. 5b). The lymph node plasma cells display uniform ergastoplasma tubes, and there are no changes of the reticular cells.

The liver parenchyma offers a uniform cytological picture — there are neither necrobiotic changes nor signs of fatty degeneration of liver cells or changes of the mitochondria. The Disse's spaces are not dilated, and the marginal cells of the sinuses are free from storage phenomena. There are no cholestatic changes either within the hepatic lobes or within the biliary tract, and the portal areas are also free from pathological changes.

The "negative findings" made for the lymph node tissue also apply to the splenic tissue.

There is no increase of lymphocytopoiesis by the lymph follicles of the spleen. The red pulp is typically hyperaemic, but otherwise there are no signs of storage phenomena or indications of increased shedding of cells.

The alveolar capillaries of the lung are free from embolic obstruction even under the transmission electron microscope. There is no widening either of the endothelium of the capillaries or of the adjacent basal membrane. Class I and Class II pneumocytes are neither widened nor enlarged, and there are no signs of increased desquamation. The pulmonary interstitium contains no inflammatory infiltrates. The structures of the bronchial walls are intact.

Transmission electron microscopy of control preparations of the myocardium of the wall of the left and right cardiac ventricles reveals a normal myocardiocyte picture; there are no dilations of the tubular system, no mitochondrial swelling, no disturbances of the myofibril pattern and no changes of the glycogen content. Both the myocardial interstice and the wall of the myocardial blood vessels are delicate.

Discussion

The roentgenological studies in dogs demonstrate clearly that, on intralymphatic use and on intracutaneous and intramucosal administration for indirect lymphography, the new water-soluble contrast medium leads to demonstration of lymphatic vessels and lymph nodes from the periphery up to the venous angle. The quality of the contrast is not inferior to that after the use of oily contrast media. Renal excretion of the new contrast medium begins even during the infusion — a phenomenon demonstrated by the occasional opacification of the pelvicalyceal system and the ureters.

By analogy to the tissue reactions elicited by oily contrast media, the morphological studies were concentrated on the injection regions with the receiving lymphatic vessels, their inner parietal layers, the thoracic duct, typical storage organs such as the liver and spleen, and the excretory organ kidney. No embolic complications were detected by studies of the

pulmonary tissue; a watch was kept for signs of intoxication above all during the studies of the fine structure of the myocardium, the liver and kidneys. The xanthomatous and giant-cell storage reactions of the lymphatic endothelium long-known under the use of oily contrast media and the pronounced histiocytic reaction within the lymph nodes following deposition of oily contrast media did not occur under the new contrast medium. Similarly, no allergic or inflammatory reactions occurred; there were also no observations of embolic complications, signs of disseminated intravascular blood coagulation or other circulatory disturbances.

A sinal structure of the lymphatic tissue with a relatively wide lumen was not caused by contact with the contrast material, but was recognized as species-specific following examination of mediastinal lymph nodes — which had not come into contact with the contrast medium — and of the lymph nodes of a control dog after an intralymphatic infusion of Ringer's lactate. Discrete bland inflammatory infiltrates in the region of the infusion sites had regressed after 1 week. No contrast medium reaction was demonstrable even by electron-microscopic examination of the lymphatic tissue of the excretory organ kidney and, in particular, no storage cells developed in the reticulo-endothelial system. Signs of intoxication such as fatty degeneration of the liver parenchyma, liver cell necroses, cholestatic changes, changes of the cardiac, hepatic and renal mitochondria, hydrops of parenchyma cells, shifts of the lysosome content in liver and kidney cells, changes of the tubular system of the myocardial cells were absent, as were also changes of the glomerular loop walls and the tubular epithelia as a morphological correlate of the excretory surfaces. In particular, no signs of osmotic nephrosis or of the occurrence of storage vacuoles in the epithelium of the main body of the kidney were observed — phenomena which have been reported following the use of another contrast medium (*Schulten* et al. 1970).

Thus, no objections arise to the use of the new contrast medium in indirect and direct lymphography from the radiological and morphological studies in dogs. The good radiological findings on intracutaneous and intramucosal administration of the contrast medium, i.e. without surgical dissection of lymphatic vessels, promise not only reduced stress for the patient, but also demonstration of lymphatic vessels and lymph nodes such as those of the neck and mediastinum, which have so far largely escaped demonstration by routine lymphography. The good local tolerance of this contrast medium also permits speculation about the visualization of the lymph flow from organs following careful infusion of the contrast medium into the organ.

Even the animal-experimental studies illustrate how decisive the examination technique can be for the success of indirect lymphography. It should be the task of clinical lymphologists of various disciplines to establish optimal administration techniques for this contrast medium in man and, hence, to unfold the clinical potential of this new diagnostic agent.

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